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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/806,036 | 07/05/2001 | Mark Leslie Smythe | 4050.001200 | 3406 |

23720 7590 08/26/2004

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| EXAMINER | |
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| KAM, CHIH MIN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/806,036 | SMYTHE ET AL. | |
| | Examiner | Art Unit | |
| | Chih-Min Kam | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8-19,32-35,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-19,32-35,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/5/01;10/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group III, claims 8-19, 32-35, 39 and 40 in the response and amendment filed June 18, 2004 is acknowledged. In the amendment, claims 1-7, 20-31, 36-38 and 41-43 have been cancelled. Regarding selecting one ring size (5, 6 or 7 atoms), one heteroatom or carbon in the ring structure, aromatic or cyclic alkyl structure, and one functional group for each X, Y and Z as A2 of general formula (a), applicant indicates such selections reflect sub-species as initial point for search and examination and further elect an aromatic ring of 6 carbon, X being oxygen, Z being carbonyl, and Y being a nitro group. As stated in the restriction requirement (see page 3, second paragraph), this selection is not a species election because each compound with different cyclic structure and functional group does not have the same specicial technical feature, thus is patentably distinct. Upon reconsideration, an aromatic ring of 6 carbon atoms; X being oxygen, sulfur, $CH_2O$- or $CH_2S$; Y being an electron-withdrawing group; Z being a group which allows the formation of a covalent carbon-nitrogen bond; and $R_3$, $R_4$ and $R_5$ being a group indicated in claim 19 will be included for examination. Therefore, claims 8-19, 32-35, 39 and 40, and an aromatic ring of 6 carbon atoms as A2 are examined.

### *Informalities*

The disclosure is objected to because of the following informalities:

2. The specification cites amino acid sequences (e.g., at page 25, lines 9 and 11; page 26, lines 9-10 and 15-16; page 31, Table 3; and others) without indicating the

sequence identifier "SEQ ID NO:", although a sequence listing for various amino acid sequences has been provided. Appropriate correction is required.

3. The specification cites cyclo-D-G-(Cat)-R-G (at page 25, lines 9 and 11) without indicating what "Cat" is, see also cyclo-[DG-Act-RG] at page 65, lines 17 and 26. Appropriate correction is required.

4. Fig. 5 is objected to because the terms of "Peptide 1d" and "Peptide 1e" are not clearly shown in the drawing. Appropriate correction is required.

***Claim Objection***

5. Claim 19 is objected to because the claim contains recitation of non-elected compounds of formula (a).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 8-19, 32-35, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8-19, 32-35, 39 and 40 are directed to a method of synthesis of a cyclic peptide or peptidomimetic compound of general formula I or II either in solution or via solid-phase synthesis by preparing a linear peptide of general formula III or XIII

containing A1 and A2, where A1 is an N-substituent or a chemical moiety that forces a cis amide bond conformation, A2 is reactive functional group to form an initial large cyclic peptide prior to ring contraction to the desired substituted cyclic peptide, and L is a linker between any atom of the peptide and the solid support. While the specification indicates the present invention is using the combination of inducing flexibility in the peptide backbone, through reversible or irreversible N-substitution or forcing cis-amide bond conformations via cis-amide bond surrogates, with novel ring contraction chemistry to preorganize peptides and facilitate the cyclization reaction in solution; and combining one or more of these preorganizing technologies with novel linkers which provide attachment between peptide and resin, to provide a solid phase strategy for the mild, efficient synthesis of cyclic peptides or cyclic peptide libraries (page 12, lines 14-25), the specification does not disclose a genus of variants for A1 and A2, and various locations of the linker L on the peptide in a method of synthesizing a cyclic peptide.

The specification indicates that A1 is reversible or irreversible N-substituents or cis-amide bond surrogates, e.g., reversible N-substituents, such as 2-hydroxy-4-methoxybenzyl (HmB), 2-hydroxybenzyl or 2-hydroxy-6-nitrobenzyl (HnB) substituents (page 16, lines 9-11; Example 1), and cis-amide bond surrogates such as tetrazole (page 24, lines 10-15); A2 may comprise a nucleophile such as thiol or hydroxyl group (page 38, scheme 6), may be any compound of General formula I described in co-pending PCT application corresponding to Australian provisional application No. PP6165 (page 16, lines 12-26), e.g., 5-nitro-2-hydroxybenzyl (HnB, Example 2); and the use of HnB as a backbone substituent and a ring contraction moiety for cyclic peptide synthesis in solution (Example 3), or on the solid support, where an activated linker or a safety catch

linker is used to attach the peptide to the resin at C-terminus carboxyl group (Example 8), or a backbone linker is used to anchor the peptide to the resin at first N-amide of C-terminus (Example 11). However, the specification does not describe a genus of variants for A1 and A2, and various locations of the linker L on the peptide in the synthesis of cyclic peptide. A species of A1 (e.g., HmB, HnB) and A2 (e.g., thiol, HnB), and a specific location of a linker (e.g., an activated linker or a safety catch linker at C-terminus carboxyl group and N-amide backbone linker of C-terminus) do not provide original descriptive support for a genus of A1 and A2, and various locations of L on the peptide in the synthesis of cyclic peptide. The variant compounds of A1 and A2 do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Applicants have described specific examples of reversible N-substituents (e.g., HmB, HnB) as A1 and a nucleophile (thiol or hydroxyl group) or HnB as A2, and a linker at N-amide backbone or carboxyl of C-terminus, however, a genus of variants for A1 and A2, and various locations of L on the peptide have not been described nor disclosed.

The skilled artisan cannot envision all the contemplated compounds based upon the general suggestion of a functional characteristic of A1 and A2, and all possible

locations of L on the peptide. The detailed structure must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

The claims are drawn to a method of synthesis of a cyclic peptide or peptidomimetic compound of general formula I or II either in solution or via solid-phase synthesis by preparing a linear peptide of general formula III or XIII containing A1 and A2, where A1 is an N-substituent or a chemical moiety that forces a cis amide bond conformation, and A2 is reactive functional group to form an initial large cyclic peptide prior to ring contraction to the desired substituted cyclic peptide, and L is a linker between any atom of the peptide and the solid support, however, the specification does not provide original descriptive support over the instantly claimed genus of variants for A1 and A2, and for various locations of L on the peptide.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim

Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 8-19, 32-35, 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 8-19 are indefinite because the claims are dependent from a canceled claim, claim 1, and do not cite the limitation of claim 1. Claims 9-19 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

9. Claims 8-19, 32 and 39 are indefinite because of the use of the terms "P is a linear peptide of 1 to 15 monomers" and "which may occur spontaneously". The terms cited render the claim indefinite, it is not clear how a peptide can be only one monomer, while the specification indicates that "monomer" includes compounds which have an amino and carboxy terminus separated in a 1,2; 1,3; 1,4 or larger substitution pattern, e.g., the 20 naturally occurring α-amino acids, and a peptide is comprised of between one and 15 monomers (page 22, line 21-24). It is also not clear whether the ring contraction reaction occurs spontaneously as the initial formation of a larger flexible ring or not as to "which may occur spontaneously". Claims 9-19 and 39 are included in the rejection because

they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

10. Claim 8 recites the limitation "General Formula I" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. See also claim 32.

11. Claims 11 and 12 are indefinite because of the use of the term "and/or". The term "and/or" renders the claim indefinite, it is unclear whether the limitation after "and/or" is included or not, and if included is to be read as an alternative "or" or the conjunctive "and".

12. Claim 12 is indefinite because of the use of the term "derivatized". The term cited renders the claim indefinite, it is not clear what chemical procedure is carried out as to "derivatized", and what compound is produced and how different the product is from the parent compound.

13. Claim 18 is indefinite because of the use of the term "A2 is an irreversible substituent, is removed.....upon ring contraction". The term cited renders the claim indefinite, it is not clear how can A2 be removed after ring contraction or eliminated upon ring contraction since A2 is an irreversible substituent, which by definition is irreversibly linked to the peptide, e.g., ethane thiol group (see page 38, lines 13-14).

14. Claims 32 and 39 are indefinite because of the use of the term "A1 is one or more N-substituents, either reversible or non-reversible, on the peptide backbone". The term cited renders the claim indefinite, it is not clear how can A1 be cleaved to form General Formula I in the case of A1 being a non-reversible substituent, which by definition is irreversibly linked to the peptide. Claim 39 is included in the rejection because it is

dependent on a rejected claim and does not correct the deficiency of the claim from which it depends.

15. Claim 33 recites the limitation "General Formula XIII" in line 2, and "General Formula I" in line 2 of step e). There is insufficient antecedent basis for this limitation in the claim.

16. Claims 33-35 and 40 are indefinite because the claim does not define the terms "A1", "A2", "P" and "L" in General Formula XV, it is not clear what the term represents. Claim 33 is also indefinite because of the use of the term "which may occur spontaneously". The term cited renders the claim indefinite, it is not clear whether the ring contraction reaction occurs spontaneously as the initial formation of a larger flexible ring or not as to "which may occur spontaneously". Claims 34, 35 and 40 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

***Conclusion***

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
August 19, 2004